Summary of Safety and Effectiveness Data

for Supplemental Application

HeartMate® Vented Electric Left Ventricular Assist System (VE LVAS)

1 General Information

Device Generic Name:	Left Ventricular Assist System
Device Trade Name:	HeartMate VE LVAS
Applicant's Name and Address:	Thermo Cardiosystems Inc 470 Wildwood Street P.O. Box 2697 Woburn, Massachusetts 01888-2697
PMA Number:	P920014/S07
Date of Notice of Approval to Applicant:	September 29, 1998

This device was originally approved in its pneumatic powered configuration (HeartMate IP LVAS) on September 30, 1994 as a bridge to cardiac transplantation. The sponsor has submitted this supplement for the HeartMate VE LVAS to allow use of a portable electrically powered configuration of the device.

The preclinical test results that apply to this modification were presented in the original application and are not repeated here. For information on the data, which were used to support the original device configuration, the summary of safety and effectiveness for the original PMA should be referenced. Written requests for copies can be obtained from the Dockets Management Branch (HFZ-305), Food and Drug Administration, 12420 Parklawn drive, Rm. 1-23, Rockville, MD 20857, under Docket 94M0404 or through the Internet at http:\\www.fda.gov\cdrh\pmapage.html.

2 Indications and Usage

The HeartMate® VE LVAS is intended for use as a bridge to transplantation in cardiac transplant candidates at risk of imminent death from nonreversible left ventricular failure. The HeartMate VE LVAS is indicated for use both inside and outside the hospital.

3 Contraindications

The patient is considered unsuitable for implant of the VE LVAS if his/her body surface area is less than 1.5 m^2.

4 Warnings and Precautions

See WARNINGS AND PRECAUTIONS in the final draft labeling (Information for Use)

5 Device Description

The HeartMate Vented Electric Left Ventricular Assist System (VE LVAS) consists of an implanted blood pump, external System Controller and external power supply components. The blood pump (Left Ventricular Assist Device or LVAD) is a pusher-plate type device that is capable of producing a stroke volume of 83 ml, generating approximately 10 liters of blood flow per minute, and a beat rate up to 120 bpm. The pump consists of a rigid titanium housing divided in half by a flexible diaphragm. One half functions as the blood chamber, while the opposite half serves as a chamber for the electric motor. This motor chamber is connected to the external control and power components via a percutaneous tube. Displacement of the diaphragm by rotation of the electric motor results in pumping of the blood.

The System Controller is a microprocessor-based unit that initiates motor actuation, monitors and reports on system function, and serves as the primary interface with the system. The System Controller provides two modes of operation, either a fixed beat rate mode or a variable beat rate mode that responds to physiologic demand.

LVAD function is adjusted by a switch-panel located on the top of the System Controller, or via a separate system monitor. The System Controller audible and visual alarms alert the user of a potentially dangerous condition. Alarms are sounded primarily if there are either low flow/stroke conditions or if the batteries are low (see Operating Manual for full discussion of alarms).

Operation of the Portable VE LVAS

The VE LVAS is powered through the System Controller by either a pair of wearable, rechargeable batteries, or through connection to a dedicated power supply device. An additional back-up portable power supply that can be used in periods of extended power outage is the emergency power pack, or EPP. In the event that electric motor actuation is disrupted, the VE LVAD may also be actuated by delivery of a pneumatic pulse through the percutaneous tube. This pulse can be provided by either the hand pump or a standard HeartMate Implantable Pneumatic drive console. The VE LVAS enables the patient to ambulate freely outside as well as inside the hospital.

Additional information regarding the pneumatic drive console and blood contacting components may be found in the Summary of Safety and Effectiveness for the original PMA application.

6 Alternative Practices or Procedures

There are currently three methods available for treating patients in end stage cardiac disease with nonreversible left ventricular failure while awaiting transplantation: pharmacologic agents to enhance cardiovascular function, intra-aortic balloon pumps for short term mechanical circulatory support, and other commercially available electromechanical ventricular assist devices.

7 Marketing History

This system configuration has been marketed since 1994 in Argentina, Australia, Belgium, Brazil, Denmark, France, Germany, Greece, India, Israel, Italy, Japan, Korea, The Netherlands, Saudi Arabia, Spain, Sweden, Taiwan R.O.C., the United Kingdom, and Yugoslavia.

This device has not been withdrawn from marketing for any reason.

8 Adverse Events

8.1 Observed Adverse Events

Based on the clinical study of 86 patients, the risks associated with the use of the HeartMate VE LVAS include the events listed below that occurred in greater than 1% of patients (note, mechanical or electrical equipment failure did not occur). The most frequently occurring event was Hepatic Dysfunction.

- Hepatic Dysfunction (78%)
- Renal Dysfunction (49%)
- Bleeding (44%)
- Neurological Dysfunction (23%)
- Thromboembolism (6%)
- Need for Reoperation (52%)
- Infection (48%)
- Death (24%)
- Right Heart Failure (7%)
- Pulmonary Dysfunction (2%)

Note: The need for reoperation may result from bleeding, infarction, gastrointestinal complications including adhesions, perforations, tissue erosion and herniation, or to treat arrhythmias with implantation of a pacemaker.

Neurological dysfunction may result from air emboli, stroke, cerebral vascular accident, temporary ischemic attack, hypoperfusion, or other mental impairment.

Embolism may result in myocardial or other organ infarction, loss of limb(s), or other vascular obstruction. In addition, it is possible that the LVAS will produce no significant hemodynamic improvement and the patient will have been exposed to the risks of a cardiothoracic procedure.

Table 8-1 presents the number of patients, percent of patients, and the total number of events for each listed adverse event, comparing events that occurred in the IP device study versus events occurring in the VE study.

Table 8-1 Adverse Events in VE and IP Studies -- Independent of Cause

Adverse Event	VE LVAS N=86, pt. years=21.8			IP LVAS N=116, pt. years=20.1		
	Patients	Percent	Events	Patients	Percent	Events
Bleeding	38	44%	41	52	45%	66
Hemolysis	0	0%	0	7	6%	7
Infection Events	38	44%	95	53	46%	181
Thromboemobolic Events	5	6%	5	5	4%	5
Right Heart Failure	6	7%	6	22	19%	22
Reoperations	40	47%	61	59	51%	111
Renal Dysfunction	41	48%	41	67	58%	67
Hepatic Dysfunction	66	77%	66	112	97%	112
Neural Dysfunction	20	23%	23	24	21%	24
Pulmonary	2	2%	2	5	4%	5
Device Failure	0	0%	0	1	0.9%	1
Deaths	20	23%	20	45	39%	45

Table 8-2 presents the number of patients, percent of patients, and the total number of events for each listed device related adverse event, comparing events that occurred in the IP study versus events occurring exclusively in the VE study

Table 8-2 Adverse Events in IP and VE Studies – Device Related

Adverse Event	VE LVAS N=86, pt. years=21.8			IP LVAS N=116, pt. years=20.1		
	Patients	Percent	Events	Patients	Percent	Events
Bleeding	8	9%	9	11	9%	13
Hemolysis	0	0%	0	5	4%	5
Infection Events	28	33%	51	37	32%	104
Thromboemobolic Events	5	6%	5	4	3%	4
Right Heart Failure	0	0%	0	0	0%	0
Reoperations	12	14%	16	15	13%	25
Renal Dysfunction	0	0%	0	0	0%	0
Hepatic Dysfunction	0	0%	0	0	0%	0
Neural Dysfunction	7	8%	7	9	8%	9
Pulmonary Dysfunction	0	0%	0	0	0%	0
Device Failure	0	0%	0	1	0.9%	1
Deaths (device related)	0	0%	0	1	0.9%	1

Table 8-3 presents the number of patients, percent of patients, and total number of events for each listed adverse event, comparing events that occurred exclusively in Phase I versus events occurring exclusively in Phase II.

Table 8-3 Adverse Events in Phase I and Phase II -- Independent of Cause

Adverse Event	VE LVAS Phase I N=86, pt. years=11.5			VE LVAS Phase II N=46, pt. years=10.3		
	Patients	Percent	Events	Patients	Percent	Events
Bleeding	38	44%	41	2	4%	2
Hemolysis	0	0%	0	0	0%	0
Infection Events	38	44%	95	7	16%	17
Thromboembolic Events	5	6%	5	0	0%	0
Right Heart Failure	6	7%	6	0	0%	0
Reoperations	40	47%	61	8	18%	14
Renal Dysfunction	41	48%	41	1	2%	1
Hepatic Dysfunction	66	77%	66	1	2%	1
Neural Dysfunction	20	23%	23	0	0%	0
Pulmonary Dysfunction	2	2%	2	0	0%	0
Device Failures	0	0%	0	0	0%	0
Deaths	20	23%	20	1	2%	1

The substantial difference seen between rates of occurrence of some events in Phase I versus Phase II is due to the increased likelihood of an event occurring in the immediate post-operative period.

Table 8-4 presents the number of patients, percent of patients, and total number of events for each listed adverse event, comparing events that occurred exclusively in Phase I versus events occurring exclusively in Phase II.

Table 8-4 Adverse Events in Phase I and Phase II – Device Related

Adverse Event	VE LVAS Phase I N=86, pt. years=11.5			VE LVAS Phase II N=46, pt. years=10.3		
	Patients	Percent	Events	Patients	Percent	Events
Bleeding	8	9%	9	0	0%	0
Hemolysis	0	0%	0	0	0%	0
Infection Events	24	28%	34	7	15%	17
Thromboemobolic Events	5	6%	5	0	0%	0
Right Heart Failure	0	0%	0	0	0%	0
Reoperations	11	13%	14	2	4%	2
Renal Dysfunction	0	0%	0	0	0%	0
Hepatic Dysfunction	0	0%	0	0	0%	0
Neural Dysfunction	7	8%	7	0	0%	0
Pulmonary Dysfunction	0	0%	0	0	0%	0
Device Failures	0	0%	0	0	0%	0
Deaths (device related)	0	0%	0	0	0%	0

8.2 Potential Adverse Events

Adverse events (in alphabetical order) which may be associated with the use of a ventricular assist device (including those listed above).

- Bleeding
- Death
- Hepatic Dysfunction
- Infection
- Neurological Dysfunction
- Pulmonary Dysfunction
- Renal Dysfunction
- Reoperation
- Right Heart Failure
- Thromboembolism
- Wound dehiscence

9 Summary of Pre-Clinical Studies

Non-clinical laboratory studies presented in the Summary of Safety and Effectiveness for the original PMA of the pneumatic device (P920014) are equally applicable to the vented electric device configuration.

9.1 In Vitro System Testing

In vitro testing consisted of integrated system testing, electromagnetic compatibility testing, software validation, electrical safety, shock and vibration, *in-vitro* reliability testing and packaging validation. The standards used were:

- ANSI/AAMI/ISO 11135. Medical Devices – Validation & Routine Control of EO Sterilization.
- IEC 60601-1. Medical Electrical Equipment part 1: General Requirements for Safety.
- UL 544. Standard for Safety, Medical and Dental Equipment.

Reliability

In-vitro reliability testing of 15 VE systems began in July, 1997 (range 318-448 days). Cumulative test time of nearly 17 years (6153 days) produced no critical failures. All 15 complete systems continue on test in September, 1998, without failure.

Based on this *in-vitro* testing to a confidence interval of 90%, there is a 98% chance that this device will be free of critical failures at two months of use, and an 87% chance that this device will be free of critical failures at one year of use.

10 Summary of Clinical Studies

10.1 Objectives

The intent of the clinical study was to answer two questions: 1) is the HeartMate VE LVAS a suitable alternative for HeartMate Implantable Pneumatic (IP) LVAS as a bridge to cardiac transplantation; and 2) is it safe for use outside of the hospital? The primary study endpoints were device flow (pump index) and adverse events. Survival data were also collected.

10.2 Methods

Enrollment criteria for cardiac transplant candidates to enter the trial were:

1. Approved cardiac transplant candidate.
2. On inotropes.
3. On an intra-aortic balloon pump (if possible).
4. Left atrial pressure or pulmonary capillary wedge pressure ≥ 20 mmHg with either:
   a. Systolic blood pressure ≤ 80 mmHg, or
   b. Cardiac index of ≤ 2.0 l/min/m^2
5. With reversible end organ dysfunction.

The study group consisted of two phases. Phase I included all patients implanted with the device. Those patients eligible to leave the hospital during their wait for a transplant were entered into Phase II of the study. To enroll into Phase II, patients were at least 14 days post implant and had recovered to New York Heart Association (NYHA) functional class I or II. Patients were also required to have a trained companion in the immediate vicinity at all times upon leaving the hospital.

The 18 participating US sites contributed 86 patients as of April 30, 1997. Patients (N=12) who were subsequently found to not meet one or more of enrollment criteria were included in the analyses of adverse events. The 74 patients who met all criteria (Phase I Core patients) were included in the survival analysis and a subset (N=43) provided the pump flow data. Figure 1 details the outcomes of all patients entered into the trial.

In the 74 core patients, the average and range of LVAS support duration ranged from 2 to 316 days with a mean of 96 days. None of the 36 Phase II outpatient core patients died while participating in the program. All of these patients maintained a NYHA functional class of I or II.

Pump flow was measured using the average pump index. The average pump index was > 2 L/min/m2 throughout the trial for 70 of 74 (95%) of the core patients in Phase I and for all 36 of the core patients in Phase II. For core patients, the average pump index was 2.70 L/min/m^2 in Phase I, and was 3.05 L/min/m2 for core patients in Phase II. The average pump index in the IP study was 2.77 L/min/m^2.

10.3 Description of Patients and Gender Bias

An analysis was performed to determine if there were any differences in the safety and effectiveness results when compared as a function of gender. Recognizing that the primary function of the device is to provide hemodynamic support, the data were first analyzed to compare the pump index data (pump flow/body surface area) for the male versus female LVAS patients. The average pump index values for the females versus males were 2.96 +/- 0.81 and 3.02 +/- 0.62 l/min/m^2, respectively.

Gender bias was not observed in the selection of patients enrolled into the study. The relative distribution of males and females enrolled into the study was consistent with the normal distribution by gender of patients awaiting transplantation. According to UNOS[1], 20% of patients awaiting transplantation are women and 80% are men. The LVAS population included 23% females compared to 77% males. These data indicate that the male:female ratios for the treatment and control groups are consistent with the distribution of transplant candidates for the population as a whole.

Safety and effectiveness was further evaluated by comparing the survival rates of the females and males in the LVAS population. The survival in the female population (65%) was similar to the males (71%).

10.4 Results

Table 10-1 compares the survival to transplant for the ID and VE studies.

Table 10-1 Survival to Transplant Comparison in IP and VE Studies Includes Percent Survival and Difference at 95% Confidence Intervals

	VE LVAS Core Patients N=74	IP LVAS Core Patients N=75	Difference [95% CI]
Percent Survival to Transplant	65% (31/48*)	77% (58/75)	-12.7% [-29.3%, 3.8%]

** Excludes VE patients continuing on LVAS support.*

[1] UNOS OPTN waiting list on the last day of 1996 (from 1997 UNOS annual report)

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Table 10-2 Survival Comparison One Year Post Transplant in IP and VE Studies
Includes Percent Survival and Difference at 95% Confidence Intervals

	VE LVAS Core Patients N=31*	IP LVAS Core Patients N=58	Difference [95% CI]
Percent Survival One Year Post Transplant	74% (23/31)	86% (50/58)	-12.0% [-29.8%, 5.8%]

** For VE, number of patients who meet Phase I inclusion/exclusion criteria.*

11 Conclusions Drawn from the Studies

Preclinical *in vitro* and *in vivo* studies in this and in the in the original PMA demonstrated that the LVAS is reliable, biocompatible, sterile, non-pyrogenic, and able to perform within the design specifications and that the design meets the intended user requirements.

The HeartMate VE LVAS clinical study provides reasonable assurance that the device is a suitable alternative for the IP device, and is safe and effective for its intended use. The data also show that the VE LVAS is safe and effective in treating patients discharged from the hospital

12 Panel Recommendation

Pursuant to section 515(c)(2) of the Federal Food, Drug, and Cosmetic Act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory panel, for review and recommendation because the information in the PMA substantially duplicated information previously reviewed by this panel.

13 FDA Decision

FDA performed an inspection and found the applicant in compliance with the Quality System Regulation (21 CFR Part 820).

14 Approval Specifications

Directions for Use: See Final Draft Labeling (Information for Use)
Hazards to Health from Use of the Device: See INDICATIONS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE EVENTS in the labeling.
Post-approval Requirements and Restrictions: See Approval Order